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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

FRONDA, CHRISTIAN L

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/006,909

Applicant(s)

KEASLING ET AL.

Examiner

Christian L. Fronda

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 and 23 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-21 and 23 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 07/08/2005 has been entered.
2. Claims 1-21 and 23 are pending and under consideration in this Office Action.
3. The rejection of claims 1, 12, 22, and 23 under 35 U.S.C. 102(b) as being anticipated by Hoshino et al. (EP 0955363) has been withdrawn in view of applicants' amendments to the claims filed 07/08/2005.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

4. Claims 1-4, 6-8, 10, 12-21, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments filed 02/09/2005 have been fully considered but they are not persuasive. Applicants argue that a number of nucleotide sequences encoding various mevalonate pathway enzymes were known as of the priority date of the instant application, various mevalonate pathway enzymes from diverse organisms were functionally interchangeable in mevalonate-producing organisms and/or retained enzymatic function in non-mevalonate-producing organisms had become well accepted by those skilled in the art as of the priority date of the instant application. Applicants conclude that those skilled in the art would conclude that the inventors were in possession of the claimed invention. The Examiner respectfully disagrees for

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reasons of record as supplemented below.

In the evaluation of the claims for compliance with the written description requirement of 35 U.S.C. 112, of particular relevance is 66 FR 1099, Friday, January 5, 2001, which states:

"Eli Lilly explains that a chemical compound's name does not necessarily convey a written description of the named chemical compound, particularly when a genus of compounds is claimed. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1405. The name, if it does no more than distinguish the claimed genus from all others by function, does not satisfy the written description requirement because "it does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Thus *Eli Lilly* identified a set of circumstances in which the words of the claim did not, without more, adequately convey to others that applicants had possession of what they claimed." (see p. 1100, 1st column, line 47 to 2nd column, line 2, attached to this office action).

The claims are genus claims that are highly variant and encompass many heterologous nucleic acids with widely differing structural, chemical, biological, and physical characteristics which encode many heterologous enzymes in mevalonate pathway, such enzymes include acetoacetyl CoA thiolase, hydroxymethylglutaryl-CoA synthase, hydroxymethylglutaryl-CoA reductase, mevalonate kinase, phosphomevalonate kinase, and mevalonate pyrophosphate decarboxylase. The claims also encompass a highly variant genus of heterologous nucleic acids encoding isopentenyl pyrophosphate isomerases and a highly variant genus of heterologous nucleic acids encoding any isoprenoid-forming enzyme. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

The claims recite the functions and names of the enzymes, but do not recite any structural information such as a nucleotide sequence encoding the entire scope of mevalonate pathway enzymes. The specification describes the production of the carotenoid lycopene using an *E. coli* strain transformed with the MEVT operon of SEQ ID NO: 8 and the MBI operon of SEQ ID NO: 12 and transformation of an *E. coli* strain MEVT operon of SEQ ID NO: 8 and MEVB operon of SEQ ID NO: 9, where the MEVT and MEVB operons contain a nucleic acid of SEQ ID NO: 1 which encodes a acetoacetyl-coA thiolase, SEQ ID NO: 2 which encodes a HMG-CoA synthase, SEQ ID NO: 3 which encodes HMG-CoA reductase, SEQ ID NO: 4 which encodes mevalonate kinase, SEQ ID NO: 5 which encode phosphomevalonate kinase, and SEQ ID NO: 6

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which encode mevalonate pyrophosphate decarboxylase. The specification does not provide a written description of any other genus members other than SEQ ID NO: 1 which encodes an acetoacetyl-coA thiolase, SEQ ID NO: 2 which encodes a HMG-CoA synthase, SEQ ID NO: 3 which encodes HMG-CoA reductase, SEQ ID NO: 4 which encodes mevalonate kinase, SEQ ID NO: 5 which encodes a phosphomevalonate kinase, SEQ ID NO: 6 which encodes a mevalonate pyrophosphate decarboxylase, and SEQ ID NO: 10 which encodes isopentenyl pyrophosphate isomerase.

While the examiner acknowledges that various mevalonate pathway enzymes were known as of the priority date of the instant application and that various mevalonate pathway enzymes from diverse organisms were functionally interchangeable in mevalonate-producing organisms and/or retained enzymatic function in non-mevalonate-producing organisms; the specification and the art do not disclose any common structural feature and nucleotide sequence that is shared between members of the claimed genus. Reciting the biological sources of the enzymes in the claims does not disclose any structural feature and nucleotide sequence common to the genus of enzymes that catalyze the recited reactions.

For example, using the publicly available program *bl2seq* program from the National Center for Biotechnology Information (NCBI) website, alignment of the nucleotide sequences encoding acetoacetyl CoA thiolase from *Zea mays* (GenBank Accession No. AF113522) and acetoacetyl CoA thiolase (GenBank Accession No. S70154) cited in applicants' arguments on p.4, lines 10-17) revealed no significant similarity (see attached Blast 2 Sequence results). This program is described by Tatiana et al. (FEMS Microbiol Lett. 1999 May 15; 174(2): 247-250). Thus, the skilled artisan cannot conclude that there is a structural feature and nucleotide sequence common to the genus of nucleic acids encoding acetoacetyl CoA thiolase.

In view of the above considerations, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed genus of heterologous nucleic acids encoding enzymes in mevalonate pathway, isopentenyl pyrophosphate isomerase enzymes, and any isoprenoid-forming enzymes.

Claim 15 is rejected under the additional grounds in that the claim recites new matter. In claim 15, the limitation "further comprising reacting the polyprenyl pyrophosphate isoprenoid precursor in the presence of an isoprenoid-forming enzyme" is not supported by the original disclosure.

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Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1, 3, 4, 6-8, 10, 12-14, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J Bacteriol. 2000 Aug;182(15):4153-7) in view of Wang et al. (Accession AF119715. 22-April-1999).

Takagi et al. teach a method comprising the steps of culturing a transformed *E. coli* JM109 strain (a prokaryote that does not normally synthesize isopentenyl pyrophosphate via a mevalonate pathway) harboring a gene cluster for the mevalonate pathway from *Streptomyces* sp. Strain CL190 that is contained in the plasmid pUMV19, where the gene cluster encodes the following enzymes of the mevalonate pathway: mevalonate kinase, diphosphomevalonate decarboxylase, phosphomevalonate kinase, and HMG-CoA synthase (see entire publication, especially pp. 4154-4156).

Takagi et al. does not teach that the said *E. coli* JM109 strain is transformed with a nucleic acids encoding isopentenyl pyrophosphate isomerase,

Wang et al. teach a nucleic acid encoding isopentenyl pyrophosphate isomerase (see Accession AF119715).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Takagi et al. such that the said *E. coli* JM109 strain is transformed with the nucleic acids taught by Wang et al.. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a beneficial method that produces isopentenyl pyrophosphate (IPP). The limitations of claims 6 and 8 are within purview of one of ordinary skill in the art since it is well known that separate vectors for specific nucleic acids encoding enzymes are used for expression of enzymes in host cells.

Since the nucleic acids taught by Takagi et al. and Wang et al. encode the enzymes recited in claim 10, the Examiner takes the position that the encoded enzymes have the same activity and amino acid sequences of the recited enzymes from *Ralstonia*, *Saccharomyces*, *Escherichia coli*,

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Blattella, *Sulfolobus*, and/or *Haloferax*. Since the Patent Office does not have the facilities for examining and comparing the recited nucleic acids encoding the recited enzymes to the prior art nucleic acids and their encoded enzymes, the burden is on applicant to show that the prior art nucleic acids are different from the recited nucleic acids. See *In re Best*, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

7. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. in view of Wang et al. as applied to claims 1, 3, 4, 6-8, 10, 12-14, 23 above; and further in view of Balbas et al. (Gene. 1996 Jun 12;172(1):65-9).

Balbas et al. teach the pBRINT family of plasmids for chromosomal integration of cloned DNA into the *E. coli* genome and method for integration of cloned DNA into the *E. coli* chromosome using these plasmids (see entire publication).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the modified method of Takagi et al. such that the nucleic acids encoding the mevalonate pathway enzymes are cloned into the pBRINT family of plasmids taught by Balbas et al., which are then used in turn to integrate the nucleic acids into the said *E. coli* JM109 strain using the method taught by Balbas et al. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

8. Claims 15-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. in view of Wang et al. as applied to claims 1, 3, 4, 6-8, 10, 12-14, 23 above; and further in view of Fujisaki et al. (J Biochem (Tokyo). 1986 May;99(5):1327-37. ABSTRACT)

Fujisaki et al. teach that isopentenyl pyrophosphate isomerase, farnesyl pyrophosphate synthetase, octaprenyl pyrophosphate synthetase and undecaprenyl pyrophosphate synthetase are four enzymes in *E. coli* that in combination ensures the *in vivo* synthesis of long-chain isoprenoids in *E. coli* (see abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the modified method of Takagi et al. such that the isoprenoid precursor is reacted with the enzymes taught by Fujisaki et al. for the purpose of having a method that produces isoprenoids. In absence of facts to the contrary, the Examiner

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takes the position that the modified method of Takagi et al. would inherently produce the recited isoprenoids since the modified method of Takagi et al. comprises all recited the method steps. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.


Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF


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